

Editorial

Mild hypothermia for post-cardiac arrest syndrome: putting the evidence into practice

In the UK, approximately 100,000 people each year have a cardiac arrest. Despite improvements in hospital care and the development of new treatments for cardiac arrest, prognosis post-cardiac arrest in terms of survival and neurological outcome is poor: mortality rates vary from 65% to 95% for out-of-hospital cardiac arrest (OHCA) and 48% to 67% for in-hospital cardiac arrest (IHCA).[1] Furthermore, 6% of ICU admissions in the UK are comatose, mechanically ventilated survivors of cardiac arrest. Historically, many clinicians have believed that induced hypothermia could attenuate neuronal death and improve neurological outcome post-cardiac arrest, and, over the past decade, this view has been affirmed in RCTs, meta-analyses, and registry data. Despite evidence supporting its therapeutic potential, uptake of induced hypothermia has been slow, with only a third of potential patients estimated to be receiving this care across Europe.[2] However, recent evidence highlights that not only is this underused therapy cost effective, but also that its implementation has become more feasible and more publically recognised as a standard of care.[3][4]

The therapeutic promise of induced hypothermia was first noted in a study including comatose survivors post-OHCA.[5] Patients treated with induced mild hypothermia had improved neurological outcomes (Glasgow outcome category scale 1 or 2) and survival rates compared with retrospective normothermic matched controls.[5] Corroboration of these early findings came from two landmark multicentre RCTs published in 2002,[6][7] both of which found significant improvements in neurological outcome and mortality rates post-induced hypothermia compared with normothermic treatment (see table 1 for summary of findings). Lower than expected enrolment rates and funding issues led to premature termination of the larger of the two studies; of 3551 people assessed, only 257 met inclusion criteria.[7] Of note, the smaller of the two studies was the first RCT to report a smaller proportion of people with poor neurological outcome with hypothermia compared with normothermia.[6] On the basis of the findings from these two studies, the American Heart Association (AHA) and the European Resuscitation Council (ERC), in conjunction with the International Liaison committee on Resuscitation (ILCOR), revised their resuscitation guidelines in 2005 to recommend that mild hypothermia be considered as a treatment option for OHCA patients presenting with VF/VT: there is Level 1 evidence for the use of induced mild hypothermia in comatose survivors of OHCA caused by VF/VT.

Data recorded in web-based registries evaluating the effectiveness of hypothermic treatment seem to affirm early results on the therapeutic benefits of induced hypothermia. However, inherent limitations (such as selection bias) should be considered when drawing inferences about therapeutic interventions from registry-level data.[2] The ERC HACA Registry (originating from the HACA group) collected web-based data on the effects of induced hypothermia from 19 different sites between May 2003 and June 2005. The goal of this particular registry was evaluation of the treatment protocol for induced hypothermia, including the intervals between cardiac arrest and ROSC, and between cardiac arrest and initiation of cooling, cooling rate, and the duration of cooling.[8] The study reported that a larger proportion of people in the hypothermia group (45%) had a favourable outcome (CPC score 1–2) at hospital discharge compared with the normothermia group (32%). Although uptake has been slow, a Finnish national database investigating the implementation of therapeutic hypothermia after cardiac arrest in intensive care units suggests that its use is on the rise (an increase from 17% in 2003 to 28% in 2005).[2]

Although hypothermic treatment is beneficial in improving outcomes in OHCA, its potential benefits, if any, in other populations have yet to be shown conclusively. Considering IHCA, observational registry data and clinical trials with historical cohorts suggest that hypothermic treatment may not afford the same benefits as observed in OHCA:[9] a randomised trial of hypothermia after resuscitation following in-hospital cardiac arrest is ongoing.[10] Furthermore, an addendum to the revised ILCOR guidelines suggests that induced hypothermia may be of benefit in people with an initial presenting non-shockable rhythm.[11] Many studies have shown poor outcome in these patients, who, despite return of spontaneous circulation (ROSC) and maximum care, have survival rates of 23% to 26%.[9] Worryingly, temporal trends indicate an increase in the number of initial non-shockable rhythms

at cardiac arrest over the past decade.[12] Although there is insufficient evidence regarding the use of induced hypothermia for IHCA and initial non-shockable rhythm, many centres are using therapeutic hypothermia in these populations.[13] As with any treatment, complications of induced hypothermia treatment are inevitable. Induced hypothermia is associated with a risk of coagulopathy, electrolyte disorders, dysrhythmias, cardiovascular instability, hyperamylasaemia, insulin resistance, and secondary increased sepsis rates.[14] although these adverse effects are rare.[7][15] Registry data also indicate that mild hypothermia is a safe treatment.

A key factor in improving probability of a positive outcome of treatment with hypothermia is speed of induction, with evidence suggesting that cooling should begin as early as possible in the post-cardiac arrest patient: animal studies have indicated a loss of benefit associated with a delay of induced hypothermia.[15][16] Ideally, for OHCA, cooling should commence in the pre-hospital environment. Surface cooling is a slow technique to decrease body temperature. Most hypothermia protocols recommend initiation of cooling through IV infusion of cold Ringer's lactate solution. This simple, inexpensive cooling technique can be applied in the pre-hospital setting, and has been shown to be safe and effective,[17] with beneficial effects on haemodynamic, renal, and acid-base indices. Once the body has reached the optimum hypothermic temperature, precise temperature control is important. Passive "rewarming" can lead to rebound hyperthermia, which adversely affects the post-anoxic brain, whereas cooling below 32 °C has been shown to exacerbate the side effects of hypothermia.[18] External devices (for example, cooling mattresses [TheraKool] or icepacks in the axilla and groin)[6][7] are used in most centres to maintain hypothermic temperatures, despite evidence that target temperature is achieved in only a third of subjects.[19] Alternative cooling devices can be used intravascularly. Although intravascular devices enable tighter temperature control than external devices, they are associated with increased expense, and possible increased risk of catheter-related bacteraemia.

The implementation of a protocol for care of the comatose post-cardiac arrest patient has led to improvement in outcomes over the past decade.[11][20] Consideration of these improvements, together with recommendations supporting its implementation, raise questions as to why induced hypothermia is not more widely used. Practical difficulties posed in setting up a department to offer induced hypothermia, and complications associated with hypothermia (including hypomagnesaemia, hypokalaemia, and bacteraemia), are thought to deter clinicians from using induced hypothermia. However, most adverse effects are usually remedied by increasing body temperature. If this proves ineffective, adverse effects can typically be treated with simple measures in the ICU environment. Moreover, the rate of more serious side effects, such as bleeding, arrhythmias, and sepsis, seen with hypothermia approximate to the rates seen in people not exposed to hypothermia. Finally, one of the core reasons may be that the evidence base was generally perceived as too weak to support implementation of hypothermia as a standard treatment.

Today, for unconscious victims of VF cardiac arrests, therapeutic hypothermia should be a standard of post-cardiac arrest care. With further supporting evidence from international data registries and clinical trials, the debate regarding the lack of evidence for this therapy is over. Evidence suggests that through implementation of a protocol incorporating, for example, better pre-hospital care, early coronary reperfusion, controlled mechanical ventilation, and therapeutic hypothermia, mortality and quality-of-life post-cardiac arrest syndrome can be improved.[20] The implementation of internationally recognised post-cardiac arrest protocol will help to improve the uptake of therapeutic hypothermia. In an area in which past clinical outcomes have been depressingly poor, there is now an opportunity to make a real change.

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Table 1: Improvements in neurological outcome and mortality rates

Outcome	RCT 1[7] 257 people resuscitated post-VF arrest		Effect size	RCT 2[6] 77 people post-VF arrest with ROSC		Effect size
	Induced hypothermia	Normothermic treatment		Induced hypothermia	Normothermic treatment	
Improved neurological outcome (proportion of people)	75/136 (55%)	54/137 (39%)	RR 1.40, 95% CI 1.08 to 1.81, P = 0.009*	21/43 (49%)	9/34 (26%)	P = 0.046
Mortality (proportion of people)	56/137 (41%)	76/138 (55%)	RR 0.74, 95% CI 0.58 to 0.95 P = 0.02**	22/43 (51%)	23/34 (68%)	P = 0.145

NNT, number needed to treat
 *NNT of 6 to prevent 1 unfavourable neurological outcome
 **NNT of 7 to save 1 life

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